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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,435	11/26/2003	Weihong Xiong	01121-17272	6215

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1611	

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09/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,435	XIONG ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2008* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-84,86-97,102 and 103* is/are pending in the application.

4a) Of the above claim(s) *53-80 and 87-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-84,86,102 and 103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The receipt is acknowledged of applicants' amendment filed 06/13/2008.

Claims 1-52, 85, 98-101 have been canceled.

Claims 53-84, 86-97, 102-103 are pending.

1. This application contains claims 53-80, 87-97drawn to an invention nonelected without traverse in the reply filed on 06/21/2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 81-84, 86, 102, and 103 are included in the prosecution.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 81-84, 86, 102, and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,352,715 ('715) with the effective filing date February 19, 1998 in view of US 6,365,178 ('178) with the effective filing date September 08, 1998.

US '715 teaches a transdermal drug delivery system to administer huperzine A in a controlled release skin patch designed for once-a-week application to treat Alzheimer disease (AD) (abstract; col.3, lines 55-65; col.4, lines 7-15; col.9, lines 1-7, 31). The patch comprises polyacrylate adhesive layer containing huperzine (col.9, lines 32-35; col.14, lines 65-67). The reference suggests the use of co-solvents to increase skin permeability of huperzine A (col.8, lines 65-67).

However, US '715 does not teach the blood plasma levels of huperzine provided by the transdermal system as instantly claimed.

The blood plasma levels are controlled by the amount of the drug included in the system as well as by the ingredients of the transdermal formulation used to deliver the

huperzine such as the type of the adhesive, the permeation enhancers and other additives in the formulation.

Therefore, the claimed blood plasma levels of huperzine can be determined by one having ordinary skill in the art by manipulating the transdermal formulation containing the huperzine and the structure of the transdermal device delivering it. Additionally, individual patient-need is also a controlling factor in determination of the dose of huperzine.

It has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller,* 105 USPQ 233.

US '175 does not explicitly teach the transdermal device comprises adhesive matrix and specific permeation enhancer as instantly claimed by claim 81.

US '178 teaches transdermal delivery device having adhesive matrix wherein the physical stability of the drug in the matrix is excellent and crystallization of the drug is inhibited (abstract). The adhesive matrix is suitable to deliver antiparkinsonism drugs and anticholinergic drugs (col.6, lines 18-20). The adhesive matrix comprises acrylic or rubber adhesives and permeation enhancer including fatty acid esters including lauryl lactate (col.6, line 42; col.7, lines 45-65; col.22, lines 36-38).

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal drug delivery system to deliver huperzine to treat patients suffering from AD wherein the system comprises polyacrylate adhesive and may contain permeation enhancer as disclosed by US '715, and provide huperzine

in adhesive matrix comprising permeation enhancer including fatty acid ester of lactic acid as disclosed by US '178 because US '715 disclosed huperzine as being capable to be provided combined with acrylic materials and enhancers and because US '178 teaches polyacrylate adhesive matrix comprising enhancers is suitable to deliver antiparkinsonism and anticholinergic drugs while such adhesive matrix shows excellent physical stability of the included drugs and inhibition of their crystallization, with reasonable expectation of having a transdermal delivery system to treat AD comprising huperzine in adhesive matrix comprising acrylate or rubber adhesive and fatty acid ester permeation enhancer wherein the matrix has excellent physical stability of the drug in the matrix without drug crystallization to provide the desired blood plasma levels of huperzine for extended time to treat the AD patients with great success.

Response to Arguments

5. Applicant's arguments filed 06/13/2008 have been fully considered but they are not persuasive.

Applicants argue that US '715 teaches adjusting pH to enhance the delivery of huperzine, and co-solvents are suggested as possibly improving the penetration of neutral forms of huperzine. Applicants argue that US '715 teaches away from the idea that the co-solvents are used as "permeation enhancers" because US 715 states that "these agents [co-solvents] also reduce partitioning [i.e. permeation] of drugs into the skin." U.S. '715 not only fails to teach the use of co-solvents as permeation enhancers,

the reference warns against the indiscriminant use of such co-solvents as they can negatively effect permeation of the drug into the skin.

In response to these argument, it is argued that US '715 suggested permeation enhancers and stated at col.8, lines 65-67 that: "A reservoir formulation or using a combination of co-solvents to increase the skin permeability of neutral Hup A could be a viable approach." Therefore the reference suggested permeation enhancers as viable approach, and this would have suggested to one having ordinary skill in the art to add permeation enhancer to the transdermal patch comprising adhesive and delivering huperzine. US '715 therefore does not teach away. It has been held that "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley,* 27 F.3d 551,553 (Fed. Cir. 1994).

Applicants argue that US '715 teaches liquid reservoir and not adhesive matrix as instantly claimed.

In response to this argument, it is noticed that reference teaches adhesive matrix at col.10, lines 15-30, that the solvent is evaporated from the adhesive/drug mixture.

Further, at col.12, lines 8-12, teaches that the drug is present in adhesive matrix. Adhesive matrix is therefore clearly taught by US '715.

Applicants stated that US '715 does not teach the currently claimed blood plasma levels.

In response to this argument, applicants' attention is directed to the fact that the reference disclosed the amount of the drug used in the transdermal patch in acrylate adhesive is 1.5 to 2.25% (table 2), and applicants disclosed 1-20% (examples). Further applicants disclosed in pages 21-23 that the claimed plasma level is achieved by permeation rate of huperzine to the skin between 0.01 to 15 $\mu g/cm^2/hr$, and the reference teaches effective permeation rate more than 1.46 $\mu g/cm^2/hr$ (claim 11 of the reference). It is expected the same delivery rate from similar formulation will provide the same plasma level. Therefore, those of ordinary skill in the art would have been readily optimized effective dosages and concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate dosage for treatment involving the above mentioned formulation would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed prior art.

Applicants argue that no "universal" permeation enhancer has been identified. Instead, the behavior of permeation enhancers is highly idiosyncratic; a permeation

enhancer effective for one drug may not be effective with other drugs, including closely related drugs. Many potential permeation enhancers interact adversely with other components of transdermal devices. US '178 teaches long list of possible drugs delivered by adhesive matrix and laundry list of possible permeation enhancer and lauryl lactate is used in combination with drug that are distinct from huperzine.

In response to this argument, it is argued that in considering the disclosure of the reference, it is proper to take into account not only the specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968). The rational to modify or to combine the prior art does not have to be expressly stated in the prior art; the rational may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve different problem. It is not necessary that the prior art suggest the combination or modification to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972). US '178 teaches anticholinergic and antiparkisonian drugs, and further suggested lauryl lactate with other drugs. However, it has been held that the disclosed examples and preferred embodiment do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Applicants argue that one having ordinary skill in the art would not combine the teaching of US '715 and US '178, and one would not select lauryl lactate from US '178.

In response to this argument, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal drug delivery system to deliver huperzine to treat patients suffering from AD wherein the system comprises polyacrylate adhesive and may contain permeation enhancer as disclosed by US '715, and provide huperzine in adhesive matrix comprising permeation enhancer including fatty acid ester of lactic acid as disclosed by US '178 because US '715 disclosed huperzine as being capable to be provided combined with acrylic materials and enhancers and because US '178 teaches polyacrylate adhesive matrix comprising enhancers is suitable to deliver antiparkinsonism and anticholinergic drugs while such adhesive matrix shows excellent physical stability of the included drugs and inhibition of their crystallization, with reasonable expectation of having a transdermal delivery system to treat AD comprising huperzine in adhesive matrix comprising acrylate or rubber adhesive and fatty acid ester permeation enhancer wherein the matrix has excellent physical stability of the drug in the matrix without drug crystallization to provide the desired blood plasma levels of

huperzine for extended time to treat the AD patients with great success. It has been held that "When a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR Int 'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007) (quoting *Sakraida v. AG Pro, Inc.,* 425 U.S. 273,282 (1976)). "When the question is whether a patent claiming the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." A conclusion of obviousness under 35 U.S.C. 103 (a) does not require absolute predictability, only a reasonable expectation of success; and references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosure. *In re Bozek*, 163 USPQ 545 (CCPA 1969).

Applicants argue that the combination of the references would be necessary based on impermissible hindsight.

In response to this argument, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the light of the foregoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the claims would have been *prima facie* obvious within the meaning of 35 U.S.C. 103 (a).

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis A. Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571) 272-0614. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Isis A Ghali/
Primary Examiner, Art Unit 1611

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